



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61K 37/00, 31/66, 31/045, 47/00, 9/36</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 94/12200</b> <b>(43) International Publication Date:</b> 9 June 1994 (09.06.94)
<b>(21) International Application Number:</b> PCT/US93/11172 <b>(22) International Filing Date:</b> 17 November 1993 (17.11.93) <b>(30) Priority Data:</b> 984,399 2 December 1992 (02.12.92) US <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US 984,399 (CIP) Filed on 2 December 1992 (02.12.92) <b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> BECHARD, Simon, R. [CA/CA]; 1755 Marchand, Laval, Quebec H7G 4V7 (CA). KRAMER, Kenneth, A. [US/US]; 426 Sterners Road, Green Lane, PA 18054 (US). KATDARE, Ashok, V. [US/US]; 801 East Fornance Street, Norristown, PA 19401 (US). <b>(74) Agent:</b> WINOKUR, Melvin; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		<b>(81) Designated States:</b> AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS  <b>(57) Abstract</b>  Pharmaceutical compositions of bisphosphonic acids, and salts thereof, are prepared by direct compression/dry mix tablet formulation. These pharmaceutical compositions are useful in the treatment of disturbances involving calcium or phosphate metabolism, in particular, the treatment and prevention of diseases involving bone resorption, especially osteoporosis, Paget's disease, malignant hypercalcaemia, and metastatic bone disease.		

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TITLE OF THE INVENTION

## DRY MIX FORMULATION FOR BISPHOSPHONIC ACIDS

BACKGROUND OF THE INVENTION

5           The pharmaceutical industry employs various methods for compounding pharmaceutical agents in tablet formulations. In particular, wet granulation is one of the most prevalent methods.

          A variety of bisphosphonic acids have been disclosed as being useful in the treatment and prevention of diseases involving bone  
10       resorption. Representative examples may be found in the following: U.S. Patent No. 3,962,432; U.S. Patent No. 4,054,598; U.S. Patent No. 4,267,108; U.S. Patent No. 4,327,039; U.S. Patent No. 4,621,077; U.S. Patent No. 4,624,947; U.S. Patent No. 4,746,654; U.S. Patent No. 4,922,077; and EPO Patent Pub. No. 0,252,504. Standard methods for  
15       tablet formulation of bisphosphonic acids, however, suffer serious difficulties.

          In particular, bisphosphonic acids which bear a basic nitrogen-containing functionality may interact with the lactose of standard formulations resulting in discoloration, instability and potency  
20       loss. This degradation of the active ingredient is particularly pronounced in the presence of water and/or elevated temperature. It is speculated that this incompatibility is specifically due to the Maillard (or "browning") reaction in which the free amino group of the  
25       bisphosphonic acid reacts with the "glycosidic" hydroxyl group of a sugar (such as lactose) ultimately resulting in the formation of brown pigmented degradates. Although this problem may be avoided by the elimination of lactose, the use of lactose as an inert diluent is generally desirable.

30           The present invention solves this problem by providing a tablet formulation and process therefor that avoids such interaction between the bisphosphonic acid and the lactose in the formulation. In addition, the present invention also provides a processing advantage since it requires only blending of the ingredients without granulation or addition of water prior to compression.

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### DESCRIPTION OF THE INVENTION

The present invention is directed in a first embodiment to a process for the preparation of pharmaceutical compositions of bisphosphonic acids by direct compression (dry mix) tablet formulation. This process employs a blend of a bisphosphonic acid and minimal amounts of other processing aids with no water added. The tablet formulation is prepared by mixing the formulation ingredients with no hydration (i.e. no additional water is added to the mixture) prior to direct compression.

More specifically, this embodiment of the present invention concerns a process for the preparation of a tablet containing a bisphosphonic acid as an active ingredient which process comprises:

- forming a mixture by mixing the active ingredient with:
  - a diluent,
  - a dry binder,
  - a disintegrant,
- and optionally one or more additional ingredients selected from the group consisting of: compression aids, flavors, flavor enhancers, sweeteners and preservatives;
- lubricating the mixture with a lubricant; and
- compressing the resultant lubricated mixture into a desired tablet form.

The disclosed process may be used to prepare solid dosage forms, particularly tablets, for medicinal administration.

Preferred diluents include lactose. In particular, anhydrous lactose is preferred from the flow processing point of view, although hydrous fast flow lactose may also be employed.

A preferred dry binder is cellulose. In particular, microcrystalline cellulose is preferred. Microcrystalline cellulose is available commercially under the trade name "Avicel" from FMC Corporation.

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The disintegrant may be one of several modified starches or modified cellulose polymers, in particular, crosscarmellose sodium is preferred. Crosscarmellose sodium NF Type A is commercially available under the trade name "Ac-di-sol".

Preferred lubricants include magnesium stearate.

Examples of the bisphosphonic acids which may be employed as active ingredients in the instant invention include:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;

3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid;

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid;

and

4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine; or a pharmaceutically acceptable salt thereof.

Methods for the preparation of bisphosphonic acids may be found in, e.g., U.S. Patent No. 3,962,432; U.S. Patent No. 4,054,598; U.S. Patent No. 4,267,108; U.S. Patent No. 4,327,039; U.S. Patent No. 4,407,761; U.S. Patent No. 4,621,077; U.S. Patent No. 4,624,947; U.S. Patent No. 4,746,654; U.S. Patent No. 4,922,077; and EPO Patent Pub. No. 0,252,504. In particular, methods for the preparation of 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid and 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid monosodium salt trihydrate may be found in U.S. Patent No. 4,407,761 and U.S. Patent No. 4,922,077, respectively.

The pharmaceutically acceptable salts of bisphosphonic acids may also be employed in the instant invention. Examples of base

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salts of bisphosphonic acids include ammonium salts, alkali metal salts such as potassium and sodium (including mono-, di- and tri-sodium) salts (which are preferred), alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D- glucamine, and salts with amino acids such as arginine, lysine, and so forth. The non-toxic, physiologically acceptable salts are preferred. The salts may be prepared by methods known in the art, such as in U.S. Patent No. 4,922,077.

In the present invention it is preferred that the bisphosphonic acid is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid. It is even more preferred that the bisphosphonic acid is a sodium salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, in particular, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

Another embodiment of the present invention is a direct compression pharmaceutical composition, such as a tablet, comprising a bisphosphonic acid, which is prepared by the disclosed process. In general, these pharmaceutical compositions comprise by weight, about 0.5 to 40% by weight of a bisphosphonic acid as an active ingredient; and from about 60 to 99.5% by weight of processing aids with no water added. More specifically, the processing aids are a diluent, a dry binder, a disintegrant and a lubricant. Preferred processing aids include: anhydrous lactose or hydrous fast flow lactose; microcrystalline cellulose; croscarmallose sodium; and magnesium stearate.

Preferred pharmaceutical compositions comprise about 0.5 to 40% by weight of a bisphosphonic acid as an active ingredient; about 10 to 80% by weight of anhydrous lactose or hydrous fast flow lactose; about 5 to 50% by weight of microcrystalline cellulose; about 0.5 to 10% by weight of croscarmallose sodium; and about 0.1 to 5% by weight of magnesium stearate.

The preferred pharmaceutical compositions are generally in the form of tablets. The tablets may be, for example, from 50 mg to

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1.0 g in net weight, more preferably 100 to 500 mg net weight, and even more preferably 200 to 300 mg net weight.

More preferred pharmaceutical compositions in accordance with the present invention comprise: about 0.5 to 25% by weight of a  
5 bisphosphonic acid selected from 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 30 to 70% by weight of anhydrous lactose or hydrous fast flow lactose; about 30 to 50% by  
10 weight of microcrystalline cellulose; about 0.5 to 5% by weight of croscarmallose sodium; and about 0.1 to 2% by weight of magnesium stearate.

Especially preferred pharmaceutical compositions comprise about 1 to 25% of the active ingredient, about 40 to 60% by weight of  
15 anhydrous lactose; about 35 to 45% by weight of microcrystalline cellulose; about 0.5 to 2% by weight of croscarmallose sodium; and about 0.1 to 1% by weight of magnesium stearate. Preferred pharmaceutical compositions as envisioned for commercial development are as follows.

Tablets of 2.5 mg potency free acid:  
20 about 1.63% by weight of 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 56.87% by weight of anhydrous lactose; about 40% by weight of microcrystalline cellulose; about 1% by weight of croscarmallose sodium; and about  
25 0.5% by weight of magnesium stearate.

Tablets of 5 mg potency free acid:  
about 3.25% by weight of 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 55.25% by  
weight of anhydrous lactose; about 40% by weight of microcrystalline  
30 cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 25 mg potency free acid:  
about 16.4% by weight of 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid monosodium salt trihydrate; about 42.1% by  
weight of anhydrous lactose; about 40% by weight of microcrystalline

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cellulose; about 1% by weight of croscarmallose sodium; and about 0.5% by weight of magnesium stearate.

Tablets of 50 mg potency free acid:

about 21.8% by weight of 4-amino-1-hydroxy-butylidene-  
1,1-bisphosphonic acid monosodium salt trihydrate; about 36.7% by  
weight of anhydrous lactose; about 40% by weight of microcrystalline  
cellulose; about 1% by weight of croscarmallose sodium; and about  
0.5% by weight of magnesium stearate.

The pharmaceutical tablet compositions of the present  
invention may also contain one or more additional formulation  
ingredients may be selected from a wide variety of excipients known in  
the pharmaceutical formulation art. According to the desired properties  
of the tablet, any number of ingredients may be selected, alone or in  
combination, based upon their known uses in preparing tablet  
compositions. Such ingredients include, but are not limited to, diluents,  
compression aids, disintegrants, lubricants, binders, flavors, flavor  
enhancers, sweetener and preservatives.

The term "tablet" as used herein is intended to encompass  
compressed pharmaceutical dosage formulations of all shapes and sizes,  
whether coated or uncoated. Substances which may be used for coating  
include hydroxypropylmethylcellulose, hydroxypropylcellulose,  
titanium oxide, talc, sweeteners, and colorants.

The pharmaceutical compositions of the present invention  
are useful in the therapeutic or prophylactic treatment of disorders in  
calcium or phosphate metabolism and associated diseases. These  
diseases can be divided into two categories:

1. Abnormal (ectopic) depositions of calcium salts,  
mostly calcium phosphate, pathological hardening of tissues and bone  
malformations.

2. Conditions which can benefit from a reduction in  
bone resorption. A reduction in bone resorption should improve the  
balance between resorption and formation, reduce bone loss or result in  
bone augmentation. A reduction in bone resorption can alleviate the



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pain associated with osteolytic lesions and reduce the incidence and/or growth of those lesions.

These diseases include: osteoporosis (including estrogen deficiency, immobilization, glucocorticoid induced and senile),  
5 osteodystrophy, Paget's disease, myositis ossificans, Bechterew's disease, malignant hypercalcemia, metastatic bone disease, periodontal disease, cholelithiasis, nephrolithiasis, urolithiasis, urinary calculus, hardening of the arteries (sclerosis), arthritis, bursitis, neuritis and tetany.

10 Increased bone resorption can be accompanied by pathologically high calcium and phosphate concentrations in the plasma, which would be alleviated by use of the instant pharmaceutical compositions.

15 The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the invention.

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EXAMPLE 1

Procedure for Manufacturing 5 mg Potency Tablets of 4-Amino-1-  
hydroxybutylidene-1,1-bisphosphonic acid

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<u>Ingredients</u>		<u>Per Tablet</u>	<u>Per 4,000 Tablets</u>
10	Active ingredient (monosodium salt trihydrate)	6.55 mg	26.2 g
	Anhydrous Lactose, NF	110.45 mg	441.8 g
15	Microcrystalline Cellulose NF	80.0 mg	320.0 g
	Magnesium Stearate Impalpable Powder NF	1.00 mg	4.0 g
20	Crosscarmellose Sodium NF Type A	2.00 mg	8.0 g

25 The active ingredient (equivalent to 5 mg anhydrous free  
acid per tablet) was premixed with 1/3 of the microcrystalline cellulose  
NF and 1/2 of the anhydrous lactose NF in a ribbon blender for 5  
minutes at 20 RPM. To the premix was added the remaining 2/3 of the  
microcrystalline cellulose NF and the remaining 1/2 of the anhydrous  
lactose NF. This was blended for 10 minutes at 20 RPM.

30 Crosscarmellose sodium was added to the blended powders and mixed  
for 5 minutes at 20 RPM. Finally the magnesium stearate was added to  
the mixture by passing through a 90 mesh screen and blended for an  
additional 5 minutes at 20 RPM. The lubricated mixture was  
compressed to provide tablets of 5 mg active ingredient.

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EXAMPLE 2

Procedure for Manufacturing 2.5 mg Potency Tablets of 4-Amino-1-  
hydroxybutylidene-1,1-bisphosphonic acid

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<u>Ingredients</u>	<u>Per Tablet</u>
Active ingredient (monosodium salt trihydrate)	3.26 mg
Anhydrous Lactose, NF	113.74 mg
Microcrystalline Cellulose NF	80.0 mg
Magnesium Stearate Impalpable Powder NF	1.00 mg
Croscarmellose Sodium NF Type A	2.00 mg

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Tablets were prepared using the procedure of Example 1.

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EXAMPLE 3

Procedure for Manufacturing 10.0 mg Potency Tablets of 4-Amino-1-  
hydroxybutylidene-1,1-bisphosphonic acid

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<u>Ingredients</u>	<u>Per Tablet</u>
Active ingredient (monosodium salt trihydrate)	13.05 mg
Anhydrous Lactose, NF	103.95 mg
Microcrystalline Cellulose NF	80.0 mg
Magnesium Stearate Impalpable Powder NF	1.00 mg
Croscarmellose Sodium NF Type A	2.00 mg

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Tablets were prepared using the procedure of Example 1.

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EXAMPLE 4

Procedure for Manufacturing 40.0 mg Potency Tablets of 4-Amino-1-  
hydroxybutylidene-1,1-bisphosphonic acid

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<u>Ingredients</u>	<u>Per Tablet</u>
Active ingredient (monosodium salt trihydrate)	51.21 mg
Anhydrous Lactose, NF	64.79 mg
Microcrystalline Cellulose NF	80.0 mg
Magnesium Stearate Impalpable Powder NF	1.00 mg
Croscarmellose Sodium NF Type A	2.00 mg

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Tablets were prepared using the procedure of Example 1.

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EXAMPLE 5

Procedure for Manufacturing 25 mg Potency Tablets of 4-Amino-1-  
hydroxybutylidene-1,1-bisphosphonic acid

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		Per 4,000
<u>Ingredients</u>		<u>Per Tablet</u>
Active ingredient		131.0 g
(monosodium salt trihydrate)		
Anhydrous Lactose, NF		337.0 g
Microcrystalline		80.0 mg
Cellulose NF		320.0 g
Magnesium Stearate		1.00 mg
Impalpable Powder NF		4.0 g
Croscarmellose Sodium		2.00 mg
NF Type A		8.0 g

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Tablets were prepared using the procedure of Example 1.

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EXAMPLE 6

Procedure for Manufacturing 50 mg Potency Tablets of 4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid

5			Per 2,500
	<u>Ingredients</u>	<u>Per Tablet</u>	<u>Tablets</u>
	Active ingredient (monosodium salt trihydrate)	65.5 mg	163.75 g
10	Anhydrous Lactose, NF	110.0 mg	275.0 g
	Microcrystalline Cellulose NF	120.0 mg	300.0 g
15	Magnesium Stearate Impalpable Powder NF	1.5 mg	3.75 g
20	Croscarmellose Sodium NF Type A	3.0 mg	7.5 g

Tablets were prepared using the procedure of Example 1.

EXAMPLE 7

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Stability Studies

30 Tablet formulations of the active ingredient (equivalent to 50 mg anhydrous free 4-amino-1-hydroxy- butylidene-1,1-bisphosphonic acid per tablet) were prepared under different conditions with differing excipients. The direct compression tablets were prepared according to the procedure of Example 1 and the wet granulated tablets were prepared according to the procedure below. The tablets were subjected to stability studies under open dish conditions at 40°C/75% relative humidity. The following observations were noted:

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1. Tablet discoloration occurred within 2 weeks in formulations which were manufactured by wet granulation and contained anhydrous lactose.

2. Tablet discoloration occurred within 4 weeks in formulations which were manufactured by wet granulation and contained hydrous lactose.

3. There was no tablet discoloration after 4 weeks in formulations which manufactured as a direct compression (dry mix) formulation. Assay of the active ingredient confirmed that there was no loss of potency or formation of degradates over the same time period. Table I demonstrates the stability characteristics of the direct compression formulation as compared to a wet granulated formulation.

TABLE I

Three-Month Data of 5 mg Probe Stability Lots

(a). Direct Compression

Condition	<u>Assay, % initial</u>			
	<u>Open Dish</u>		<u>HDPE/CRC Bottle</u>	
	<u>cpd</u>	<u>Adduct</u>	<u>MK-0217</u>	<u>Adduct</u>
40°C	101.2%	----	99.8%	----
40°C/75% RH	102.9%	----	98.5%	----
			100.9%*	----
60°C	100.6%	----	101.3%	----
RT/90% RH	103.5%	----	102.1%	----

\* Duplicate value



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## (b). Wet Granulation

	<u>Condition</u>	<u>Assay, % initial</u>			
		<u>Open Dish</u>		<u>HDPE/CRC Bottle</u>	
5		<u>epd</u>	<u>Adduct</u>	<u>MK-0217</u>	<u>Adduct</u>
	40°C	99.7%	----	97.0%	----
				100.0%**	----
10	40°C/75% RH	84.1%	15.9%	94.6%	5.6%
				99.7%**	----
	60°C	92.6%	trace***	94.3%	trace***
				94.6%**	trace
	RT/90% RH	101.4%	----	100.4%	----
15				99.4%	----

\*\* With desiccant

\*\*\* Trace indicates that the adduct peak is detectable (~5%) but not quantifiable under experimental conditions.

cpd = 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid

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Process for wet granulation tablets

- 1) Anhydrous lactose, alendronate sodium and microcrystalline cellulose was mixed in a suitable size blender.
- 2) The blend was strained through mesh #30 followed by remixing for an additional time.
- 3) The powder mixture was granulated with an adequate quantity of water until caking occurred.
- 4) The wet mass was poured through a screen #5.

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5) The wet sized granulation was dried in a forced air dryer at 40-50°C until the loss on drying was less than 2% at 105°C.

5 6) The dry granulation was sized through a suitable screen.

7) The dry sized granulation was mixed with croscarmellose sodium followed by magnesium stearate.

10 8) Tablets were compressed using the labeled granulation.

15 While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

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WHAT IS CLAIMED IS:

1. A process for the preparation of a tablet containing  
an active ingredient selected from the group consisting of:
- 5 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;  
N-methyl-4-amino-1-hydroxybutylidene-1,1-bis-  
phosphonic acid;  
4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-  
bisphosphonic acid;
- 10 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;  
3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bis-  
phosphonic acid;  
1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-  
bisphosphonic acid;
- 15 1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid;  
and  
4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine;  
or a pharmaceutically acceptable salt thereof;
- 20 which process comprises:  
forming a mixture by mixing the active ingredient with:  
a diluent, selected from: anhydrous lactose and hydrous fast  
flow lactose,  
a dry binder,
- 25 a disintegrant,  
and optionally one or more additional ingredients selected  
from the group consisting of: compression aids, flavors,  
flavor enhancers, sweeteners and preservatives;  
lubricating the mixture with a lubricant; and
- 30 compressing the resultant lubricated mixture into a desired  
tablet form.
2. The process of Claim 1 wherein the active ingredient  
is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

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3. The process of Claim 1 wherein the active ingredient is 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate.

5 4. The process of Claim 1 wherein the dry binder is microcrystalline cellulose.

10 5. The process of Claim 1 wherein the disintegrant is selected from the group consisting of modified starch, modified cellulose polymer, and croscarmallose sodium, or a combination thereof.

15 6. The process of Claim 1 wherein the disintegrant is croscarmallose sodium.

7. The process of Claim 1 wherein the lubricant is magnesium stearate.

20 8. A solid dosage form containing an active ingredient selected from the group consisting of:

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;  
N-methyl-4-amino-1-hydroxybutylidene-1,1-bis-  
phosphonic acid;

25 4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bisphosphonic acid;

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;  
3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid;

30 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid;

1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid;  
and

4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine;  
or a pharmaceutically acceptable salt thereof;

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wherein the dosage form is prepared by the process of  
Claim 1.

5           9.    A pharmaceutical composition comprising by weight,  
about 0.5 to 40% by weight of an active ingredient selected from the  
group consisting of:

          4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;  
          N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic  
          acid;  
10          4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bis-  
          phosphonic acid;  
          3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;  
          3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bis-  
          phosphonic acid;  
15          1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-  
          bisphosphonic acid;  
          1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid;  
          and  
          4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine;  
20          or a pharmaceutically acceptable salt thereof;

          and from about 60 to 99.5% by weight of excipients consisting  
          essentially of: anhydrous lactose or hydrous fast flow lactose;  
25          microcrystalline cellulose; croscarmallose sodium; and magnesium  
          stearate.

          10.   A pharmaceutical composition comprising by weight,  
          about 0.5 to 40% by weight of an active ingredient selected from the  
          group consisting of:

30          4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;  
          N-methyl-4-amino-1-hydroxybutylidene-1,1-bisphosphonic  
          acid;  
          4-(N,N-dimethylamino)-1-hydroxybutylidene-1,1-bis-  
          phosphonic acid;

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3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid;  
3-(N,N-dimethylamino)-1-hydroxypropylidene-1,1-bis-  
phosphonic acid;  
1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-  
bisphosphonic acid;  
1-hydroxy-2-[3-pyridyl]ethylidene-1,1-bisphosphonic acid;  
and  
4-(hydroxymethylene-1,1-bisphosphonic acid)piperidine;  
or a pharmaceutically acceptable salt thereof;

about 10 to 80% by weight of anhydrous lactose or hydrous fast flow  
lactose;  
about 5 to 50% by weight of microcrystalline cellulose;  
about 0.5 to 10% by weight of croscarmallose sodium; and  
about 0.1 to 5% by weight of magnesium stearate.

11. The pharmaceutical composition of Claim 10  
comprising about 0.5 to 25% by weight of the active ingredient, about  
30 to 70% by weight of anhydrous lactose or hydrous fast flow lactose;  
about 30 to 50% by weight of microcrystalline cellulose; about 0.5 to  
5% by weight of croscarmallose sodium; and about 0.1 to 2% by weight  
of magnesium stearate.

12. The pharmaceutical composition of Claim 10  
wherein the active ingredient is 4-amino-1-hydroxybutylidene-1,1-  
bisphosphonic acid.

13. The pharmaceutical composition of Claim 10  
wherein the active ingredient is 4-amino-1-hydroxybutylidene-1,1-  
bisphosphonic acid monosodium salt trihydrate.

14. The pharmaceutical composition of Claim 13  
comprising about 1 to 25% by weight of the active ingredient, 4-amino-  
1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt

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trihydrate, about 40 to 60% by weight of anhydrous lactose; about 35 to 45% by weight of microcrystalline cellulose; about 0.5 to 2% by weight of croscarmallose sodium; and about 0.1 to 1% by weight of magnesium stearate.

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15. A tablet prepared from the pharmaceutical composition of Claim 13.

10 16. A tablet prepared from the pharmaceutical composition of Claim 10.

17. A process for the preparation of a table containing as active ingredient a basic nitrogen containing bisphosphonate: which process comprises:

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forming a mixture by mixing the active ingredient with:  
a diluent, selected from: anhydrous lactose and hydrous fast flow lactose,

a dry binder,

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a disintegrant,

and optionally one or more additional ingredients selected from the group consisting of: compression aids, flavors, flavor enhancers, sweeteners and preservatives;

lubricating the mixture with a lubricant; and

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compressing the resultant lubricated mixture into a desired tablet form.

18. A solid dosage form containing as active ingredient a basic nitrogen containing bisphosphonate wherein the dosage form is prepared by the process of Claim 1.

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/11172

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) :A61K 37/00, 31/66, 31/045, 47/00, 9/36

US CL :514/12, 141, 738, 786, 959, 960; 424/479.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/12, 141, 738, 786, 959, 960; 424/479.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS:

Bisphosphonate? (P) Lactose

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,942,157 (Gall et al) 17 July 1990 Column 4, lines 14-22.	1-18
Y	US, A, 5,041,428 (Isomura et al) 20 August 1991. Column 7, lines 15-50.	1-18
Y	GB,A, 1,036,368 (National Dairy Products Corporation) 20 July 1966. Page 2, lines 3-69.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be part of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

14 FEBRUARY 1994

Date of mailing of the international search report

23 FEB 1994

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